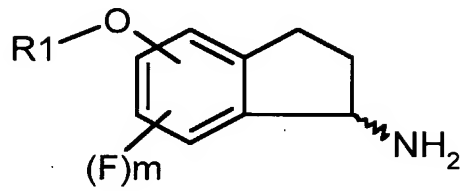
CLAIMS.

1. A process for the preparation of optically active substituted alpha-indanyl amide derivatives of formula (I) :

(I)



wherein

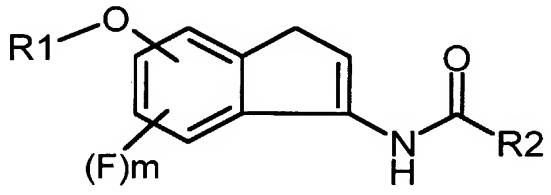
m is an integer equal to 0, 1, 2 or 3,

R_1 is a hydrogen atom, an alkyl group having from 1 to 20 carbon atoms, an aryl group having from 6 to 20 carbon atoms, an alkylaryl group having from 6 to 20 carbon atoms, an alkaloyl group, an aryloyl group,

which comprise :

- an asymmetric hydrogenation reaction of an en-amide derivative of formula (III)

(III)



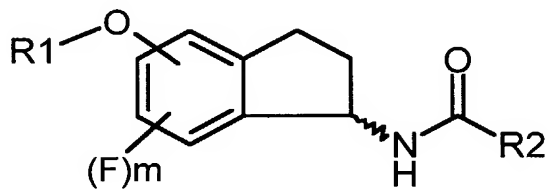
wherein m and R1 are as defined above,

R2 is a hydrogen atom, an alkyl group having from 1 to 20 carbon atoms, an aryl group having from 6 to 20 carbon atoms, an alkylaryl group having from 6 to 20 carbon atoms,

in presence of hydrogen and an optically active catalyst,

in order to obtain an amide derivative of formula (II) :

(II)



(R) ou (S)

- a hydrolysis reaction of the amide derivative of formula (II) obtained in the previous step,

in order to obtain optically active substituted alpha-indanyl amide derivatives of formula (I).

2. Process according to claim 1, wherein the optically active catalyst used in the asymmetric hydrogenation of the en-amide derivative of formula (III) is represented by a chiral phosphine transition metal complexe of formula (VIIA) :

$$M(X)_j(Z)_i(L^*)(Y)_n \qquad \text{(VIIA)}$$

wherein

M is a transition metal selected in the group comprising ruthenium (Ru), rhodium (Rh) and iridium (Ir)

X is a halogen atom selected in the group comprising chlore (Cl), brome (Br), fluor (F) and iode (I),

Z is an aryl group having from 6 to 20 carbon atoms or an unsaturated organic group, cyclic or not, selected in the group comprising olefine, diene and cyano,

L* is a chiral ligand selected in the group comprising the chiral diphosphine derivatives, the chiral atropoisomeric diphosphine derivatives, the chiral monodentate phosphoramidine derivatives, the chiral biphospholane derivatives, the chiral ferrotane derivatives and the chiral ferrocenyl phosphine derivatives,

Y is an anion such as ClO_4^-, BF_4^-, PF_6^-, SbF_6^-,

j is an integer equal to 0 or 1,

i is an integer equal to 0, 1, 2 or 4,

n is an integer equal to 1 or 2.

3. Process according to claim 1, wherein the optically active catalyst used in the asymmetric hydrogenation of the en-amide derivative of formula (III) is represented by a chiral phosphine transition metal complexe of formula (VIIB) :

$$[M(X)(L^*)]_2(X)_3 \; S \qquad \text{(VIIB)}$$

wherein

M is a transition metal selected in the group comprising ruthenium (Ru), rhodium (Rh) and iridium (Ir),

X is a halogen atom selected in the group comprising chlore (Cl), brome (Br), fluor (F) and iode (I),

L* is a chiral ligand selected in the group comprising the chiral diphosphine derivativee, the chiral atropoisomeric diphosphine derivatives, the chiral monodentate phosphoramidine derivatives, the chiral biphospholane derivatives, the chiral ferrotane derivatives and the chiral ferrocenyl phosphine derivatives,

S is a primary amine,

j is an integer equal to 0 or 1,

i is an integer equal to 0, 1, 2 or 4,

n is an integer equal to 1 or 2.

4. The process according to claim 2, wherein the olefine is selected in the group comprising pi-allyl and 1,3,5,7-cyclooctatetraene and the diene is selected in the group comprising 1,3-butadiene, 2,5-norbornadiene, 1,5-cyclooctadiene (COD) and cyclopentadiene.

5. The process according to claim 2, wherein the aryl group is a benzene optionally substituted with an alkyl.

6. The process according to any one of claims 2 or 3, wherein the chiral diphosphine is selected in the group comprising BICP, DuPHOS,

MiniPHOS, BDPMI, TangPHOS, P-PHOS, Tol-P-PHOS, Xyl-P-PHOS and BPE.

7. The process according to any of claims 2 or 3, wherein the chiral atropoisomeric diphosphine is selected in the group comprising BINAP, TolBINAP, MeOBIPHEP, BINAPO, SYNPHOS and BINAPO optionally ortho-substituted with an alkyl or an aryl.

8. The process according to any of claims 2 or 3, wherein the chiral monodentate phosphoramidine is selected in the group comprising Monophos and Ethylmonophos.

9. The process according to any of claims 2 or 3, wherein the chiral bisphospholane is selected in the group comprising Tangphos, Duphos, Me-Duphos Me-BPE, Et-BPE, Binaphane and Malphos.

10. The process according to any of claims 2 or 3, wherein the chiral ferrocenyl phosphine is JOSIPHOS.

11. The process according to any one of claims 1 to 10, wherein the optically active catalyst is $Ru(COD)(MeOBIPHEP)BF_4^-$, $Ru(COD)(BINAP)BF_4^-$ or $Rh(COD)(Me\text{-}BPE)BF4^-$.

12. The process according to any one of claims 1 to 11, wherein the solvant used during the assymetric hydrogenation is selected in the group comprising ether, aromatic hydrocarbon halogenated hydrocarbon and alcohol, preferably an alcohol.

13. The process according to claim 12, wherein the ether is selected in the group comprising tetrahydrofuran (THF), tetrahydropyran and diethyl ether, the aromatic hydrocarbon is selected in the group comprising benzene and toluene, the halogenated hydrocarbon is dichloromethane, the alcohol is selected in the group comprising methanol, ethanol and isopropanol, and is preferably the methanol.

14. The process according to any one of claims 1 to 13, wherein the molar ratio of the en-amide derivative of formula (III) to the catalyst (VII) used during the asymmetric hydrogenation is from 100/1 to 10000/1, preferably from 100/1 to 1000/1 and is more preferably from 200/1 to 1000/1.

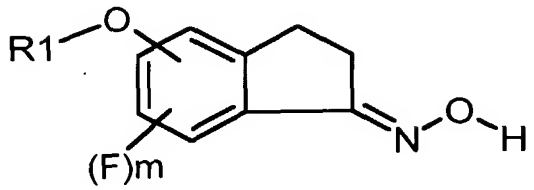
15. The process according to any one of claims 1 to 14, wherein the hydrogen pressure used during the asymmetric hydrogenation is from 0,5 to 20 bars, preferably from 0,5 to 10, and more preferably 1 to 8.

16. The process according to any one of claims 1 to 15, wherein the temperature range used during the asymmetric hydrogenation is from - 20 to 100°C, preferably from 20 to 100°C, and more preferably 20°C to 60°C.

17. The process according to any one of claims 1 to 16, wherein the en-amide derivative of formula (III) is prepared by the two following step :

- an acylation reaction of an alpha-hydroxyimino-indane derivative of formula (V):

(V)



wherein R_1 and m are as defined above

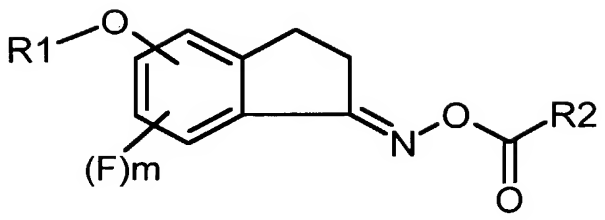
in presence of an organic anhydride of formula (VI) :

$$R_2OC^{-O}{}^{-}COR'_2 \qquad (VI)$$

wherein R2 and R'2 identical or different are a hydrogen atom, an alkyl group having from 1 to 20 carbon atoms, an aryl group having from 6 to 20 carbon atoms, an alkylaryl group having from 6 to 20 carbon atoms,

in order to obtain an N-(O-acylimino)-indane derivative of formula (IV) :

(IV)



wherein R_1, m and R_2 are as defined above,

- a hydrogenolyse-acylation reaction of the N-(O-acylimino)-indane derivative of formula (IV) obtained in the previous step,

in presence of an organic anhydride of formula (VI) as defined above and of an heterogeneous catalyst based on a metal transition selected in the group comprising Pt, Pd, Ir, Rh and Ni,

in order to obtain an en-amide derivative of formula (III).

18. The process according to claim 17, wherein the molar ratio of the organic anhydride of formula (VI) to the alpha-hydroxyimino-indane derivative of formula (V) used during the acylation reaction is from 1 : 1 to 5 : 1 and preferably 1.5 : 1 to 2: 1.

19. The process according to claim 17 or 18, wherein the heterogeneous catalyst used during the hydrogenolyse-acylation reaction of the derivative of formula (IV) is selected in the group comprising PtO_2,

Pt/C, Pd/C, $Pd(OH)_2/C$, Ir/C, Rh/C and Raney Ni, and is preferably Ir/C.

20. The process according to any one of claims 17 to 19, wherein the effective amount of the heterogeneous catalyst used during the hydrogenolyse-acylation is in an amount from 0.1% to 30% for 1 mole of the N-(O-acylimino)-indane derivative of formula (IV).

21. The process according to any one of claims 17 to 20, wherein the molar ratio of the organic anhydride of formula (VI) to the N-(O-acylimino)-indane derivative of formula (IV) used during the hydrogenolyse-acylation reaction is from 1 : 1 to 5 : 1 and preferably 1.5 : 1 to 2 : 1.

22. The process according to any one of claims 17 to 21, wherein the acylation reaction of the derivative of formula (V) and the hydrogenolyse-acylation reaction of the derivative of formula (IV) are respectively performed in an aprotic non-basic solvent selected in the group comprising ether, organic acid alkyl ester, aromatic hydrocarbon and halogenated hydrocarbon.

23. The process according to any one of claims 17 to 22, wherein the organic anhydride of formula (VI) used during the acylation reaction and the hydrogenolyse-acylation reaction is selected in the group comprising dialkyl anhydride, diaryl anhydride and alkylarylanhydride, and is preferably an acetic anhydride.

24. The process according to any one of claims 17 to 23, wherein the derivative of formula (III) is obtained directly from the derivative of formula (V) without isolating specifically the derivative of formula (IV).